Total Synthesis of Leiocarpin C and (+)-Goniodiol *via* an Olefin Cross-Metathesis Protocol

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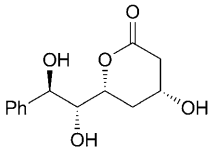
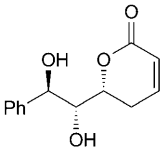
A stereoselective total synthesis of leiocarpin C (**2**) and (+)-Goniodiol (**1**) by applying olefin cross-metathesis and substrate directed dihydroxylation as the key steps is reported (*Scheme 3*).

Introduction. – Leiocarpin C (**1**) is a natural styryl lactone. Styryl lactones are natural products that exhibit significant biological activities such as antitumor, antifungal, and antibiotic properties [1]. Compound **1** was isolated from the stem bark of the tropical plant *Goniothalamus leiocarpus* [2]. Recently, two syntheses of **1** were reported [3]. (+)-Goniodiol (**2**) was isolated from the stem bark of *Goniothalamus gigantus*, and from the leaves and twigs of *Goniothalamus sesquipedalis* [4b], and it has been shown as selectively cytotoxic against human lung carcinoma cells A-549 (ED_{50} 0.12 μg/ml^{-1}) and p-388 murine leukemia cells (IC_{50} 4.56 μg ml^{-1}) [4]. Several syntheses of **2** have been already reported [3][5]. Impressed by the bio-profile of these compounds, coupled with our interest in the synthesis of such pyrone containing natural products [6], we embarked on their total synthesis. Here, we report the total synthesis of **1** and **2** by a novel methodology involving olefin cross-metathesis and dihydroxylation as the key steps to access the basic premise of the skeleton and thence its elaboration to the targets.



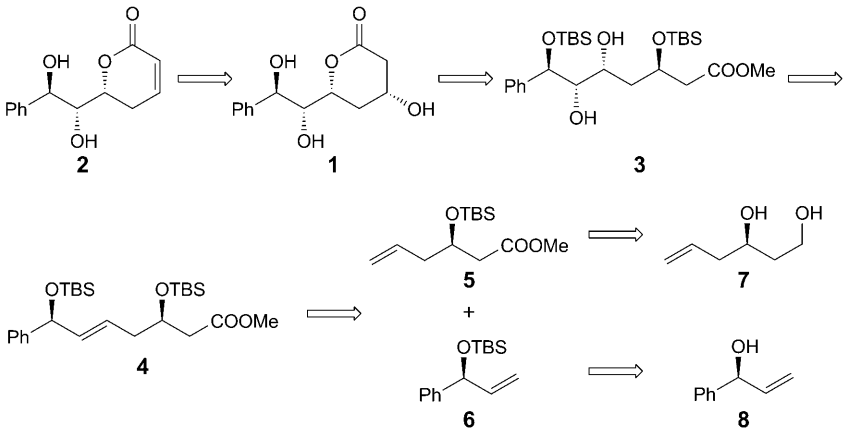
Leiocarpin C (**1**)



(+)-Goniodiol (**2**)

Retrosynthetically (*Scheme 1*), **2** could be obtained from **1** according to a reported procedure [3b]. The latter could be obtained by the desilylation/concomitant lactonization of acyclic ester **3**, which, in turn, could be prepared by the substrate-controlled dihydroxylation of the cross-metathesis product **4**. Formation of **4** could be realized from the cross-metathesis reaction of two olefinic fragments **5** and **6**. While, fragment **5** could be prepared from the known compound **7** [7a] by protection of the secondary alcohol, oxidation of the primary alcohol, and esterification of the

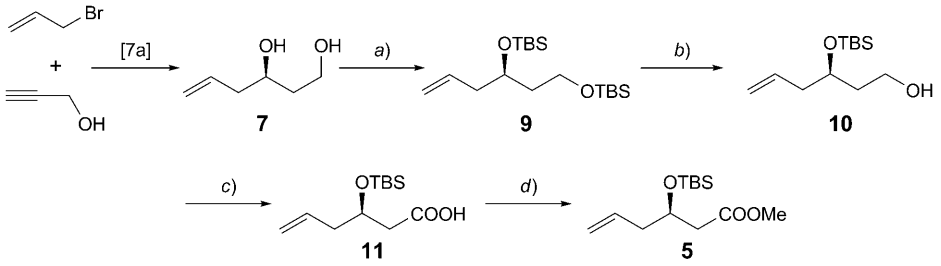
Scheme 1. *Retrosynthethic Analysis*



corresponding acid as the key steps, the other fragment **6** could be prepared by the (*t*-Bu)Me_2Si (TBS) etherification of the known (*S*)-1-phenylprop-2-en-1-ol ((*S*)-**8**) that has been earlier prepared by us [7b].

Results and Discussion. – The synthesis of **1** commenced by accessing the two fragments **5** and **6** independently. First, olefinic ester **5** was synthesized as depicted in *Scheme 2*. The secondary OH group of diol **7** was protected as its TBS ether. To differentiate between the primary and secondary alcohols, a selective deprotection of the bis-TBS ether in the primary position was employed: the bis-TBS ether **9** was formed, followed by the selective removal of the primary silyl group to afford **10** (74%). The primary alcohol **10** was oxidized to the corresponding aldehyde under *Swern* oxidation conditions, which was further oxidized [8] to the acid **11** (86% over two steps). The latter was subsequently esterified to afford **5** (85%) using CH_2N_2 in Et_2O.

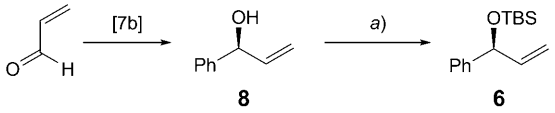
Scheme 2. *Synthesis of Fragment* **5**



a) (*t*-Bu)Me_2SiCl (TBSCl), 1*H*-imidazole, CH_2Cl_2, 0°, 2 h; 95%. *b*) TsOH, MeOH, −10°, 0.5 h; 74%. *c*) 1. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°, 1 h; 2. $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, H_2O, 0°, 3 h; 86% (overe two steps). *d*) CH_2N_2, Et_2O, 0°, 5 min; 85%.

The known methanol derivative **8** was protected (*Scheme 3*) as its silyl ether **6**. Based on our earlier results, this protection was warranted to enable a facile cross-metathesis reaction.

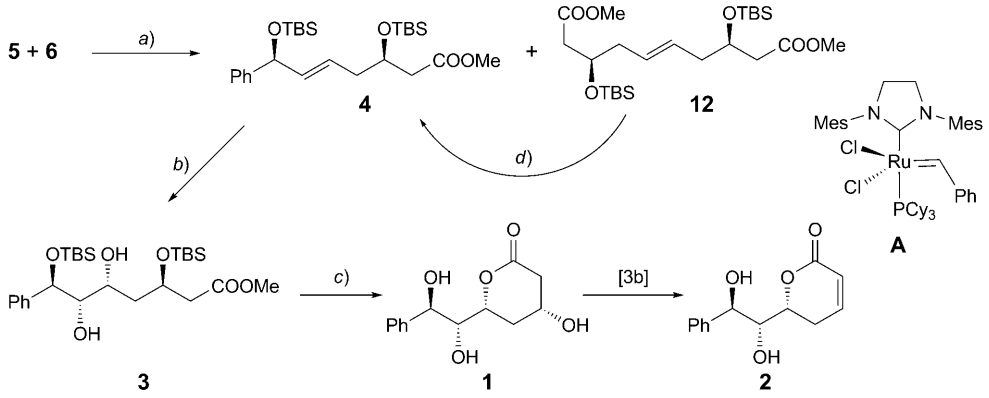
Scheme 3. *Synthesis of Fragment* **6**



a) TBSCl, 1*H*-imidazole, CH_2Cl_2, 0°, 0.5 h, 80%.

As outlined in *Scheme 4*, the crucial olefin cross-metathesis reaction [9] between olefinic ester **5** and **6** (1:1.5 ratio) using *Grubbs*-II catalyst, **A**, resulted in product **4** (60%) as a single stereoisomer and the homo-dimer **12** (5%) of **5**. Compound **12** was effectively converted to the desired olefin **4** (60%) by using a second cross-metathesis reaction with **6** under the same conditions. Subsequently, **4** was dihydroxylated [10] to give the desired diol **3** as the major isomer (75%) after column chromatography. The minor diastereoisomer was obtained in 18% yield. Diol **3** was treated with *Amberlyst 15* resin in MeCN to furnish **1** (93%). The physical and spectroscopic data of **1** were identical to the reported ones of natural leiocarpin C $[\alpha]_D^{25} = -63.1$ ($c = 0.30$, $CHCl_3$) [2][3]. Finally, **1** was converted to **2** according to the known procedure [3b]. The spectroscopic data of **2** were in agreement with those reported in [3][5].

Scheme 4



a) *Grubbs*-II (**A**, 10 mol-%), CH_2Cl_2, r.t., 24 h, 60%. *b*) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), acetone/H_2O 4:1, 24 h, 75%. *c*) *Amberlyst 15*, MeCN, r.t., 2 h, 93%. *d*) **6**, *Grubbs*-II (**A**, 10 mol-%), CH_2Cl_2, r.t., 24 h, 60%.

In summary, a stereoselective synthesis of **1** was achieved in ten steps and in 24.5% overall yield by cross-metathesis, followed by dihydroxylation as the key steps to access the advanced intermediate **3** that was endowed with all stereogenic centers and functionalities; and **3** was easily converted to the target compound **1**. Further, the synthesis of **2** was also accomplished.

Experimental Part

General. Org. solns. were dried over anh. Na_2SO_4 and concentrated below 40° *in vacuo*. Column chromatography (CC): silica gel (SiO_2; *Acme*'s, 60–120 mesh). Optical rotations : *JASCO DIP 300* digital polarimeter at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^{1}H- and ^{13}C-NMR: *Bruker Avance-300 MHz*, and *Inova 500 MHz*; 7–10 mM solns. in $CDCl_3$; TMS as internal standard; *J* values in Hz. MS: *Finnigan Mat 1210* double-focusing mass spectrometers operating at a direct inlet system.

*(5*R*)-2,2,3,3,9,9,10,10-Octamethyl-5-(prop-2-en-1-yl)-4,8-dioxa-3,9-disilaundecane* (**9**). To a stirred soln. of diol **7** [7a] (0.30 g, 2.5 mmol) in CH_2Cl_2 (3.5 ml), 1*H*-imidazole (0.7 g, 10.3 mmol) was added at 0°, and the mixture was stirred for 5 min, then TBS-Cl (0.85 g, 5.6 mmol) was added, and the stirring was continued for 2 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), and the org. layer was washed with H_2O (5 ml), followed by brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2; 1% AcOEt/hexane) to afford **9** (0.84 g, 95%). Colorless oily liquid. $[\alpha]_D^{25} = -60.4$ ($c = 0.8$, $CHCl_3$). IR (neat): 3454, 2954, 2857, 1742, 1638, 1253, 1088, 834, 776. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.03–5.86 (*m*, 1 H); 5.16 (*dd*, *J* = 1.5, 12.1, 2 H); 4.03 (*quint.*, *J* = 6.0, 1 H); 3.81 (*t*, *J* = 6.7, 2 H); 2.47–2.27 (*m*, 2 H); 1.83–1.71 (*m*, 2 H); 1.05 (*s*, 18 H); 0.21 (*s*, 6 H); 0.19 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 135.0; 116.9; 68.7; 59.6; 42.2; 39.7; 26.1 (6 C); 18.1 (2 C); −4.1 (2 C); −5.1 (2 C). ESI-MS: 345 (71, $[M+H]^+$), 367 (100, $[M+Na]^+$).

*(3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hex-5-en-1-ol* (**10**). To a stirred soln. of **9** (0.82 g, 2.38 mmol) in dry MeOH (10 ml), TsOH (0.04 g, 0.17 mmol) was added at −10°, and the mixture was stirred for 0.5 h. The reaction was quenched with 1.5 ml of Et_3N, the solvent was evaporated, the residue was dissolved in AcOEt (2 × 5 ml), and washed with H_2O (6 ml), and brine (6 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2; 10% AcOEt/hexane) to afford **10** (0.40 g, 74%). Syrupy liquid. $[\alpha]_D^{25} = -64.4$ ($c = 0.85$, $CHCl_3$). IR (neat): 3380, 2932, 2858, 1740, 1640, 1253, 1068, 835, 774. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.82–5.67 (*m*, 1 H); 5.06 (*d*, *J* = 4.1, 1 H); 5.01 (*s*, 1 H); 3.99–3.91 (*m*, 1 H); 3.83–3.72 (*m*, 1 H); 3.70–3.61 (*m*, 1 H); 2.28 (*t*, *J* = 6.2, 2 H); 1.82–1.72 (*m*, 1 H); 1.67–1.56 (*m*, 1 H); 0.89 (*m*, 9 H); 0.09 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.4; 117.3; 71.1; 60.0; 41.6; 37.6; 25.7; 17.9; −4.4; −4.8. ESI-MS: 231 (23, $[M+H]^+$), 253 (100, $[M+Na]^+$). HR-MS: 253.1601 ($C_{12}H_{26}NaO_2Si^+$; calc. 253.1599).

*(3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hex-5-enoic Acid* (**11**). To a soln. of oxalyl chloride (0.28 ml, 2.47 mmol) in dry CH_2Cl_2 (3 ml) at −78°, dry DMSO (0.27 ml, 4.95 mmol) was added dropwise and stirred for 10 min. A soln. of **10** (0.38 g, 1.65 mmol) in dry CH_2Cl_2 (2 ml) was added, and the mixture was stirred for 1 h at −78°. The reaction was quenched with Et_3N (1.28 ml, 9.9 mmol), and the mixture was diluted with CH_2Cl_2 (5 ml), washed with H_2O (4 ml) and brine (4 ml), dried (Na_2SO_4), and evaporated to furnish the corresponding aldehyde. To a cooled (0°) soln. of the above aldehyde (0.38 g, 1.65 mmol) in *t*-BuOH (2 ml), 2-methylbut-2-ene (1 ml), followed by a soln. of $NaClO_2$ (0.3 g, 3.3 mmol) and NaH_2PO_4 (0.51 g, 3.3 mmol) in H_2O (1 ml), was added, and the mixture was stirred at r.t. for 3 h. The solvent was evaporated, the residue was dissolved in AcOEt (5 ml) and washed with H_2O (5 ml) and brine (5 ml), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue by CC (SiO_2; 12% AcOEt/hexane) gave **11** (0.34 g, 86% over two steps). Yellow syrup. $[\alpha]_D^{25} = -48.2$ ($c = 0.7$, $CHCl_3$). IR (neat): 3380, 2932, 2858, 1740, 1640, 1253, 1068, 835, 774. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.84–5.67 (*m*, 1 H); 5.09 (*s*, 1 H); 5.05 (*d*, *J* = 3.5, 1 H); 4.18 (*quint.*, *J* = 5.6, 1 H); 2.51–2.37 (*m*, 2 H); 2.27 (*pseudo-t*, *J* = 6.2, 2 H); 0.86 (*s*, 9 H); 0.07 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.3; 133.7; 118.0; 68.8; 41.9; 41.7; 25.7; 17.9; −4.5; −4.9. ESI-MS: 245 (26, $[M+H]^+$), 267 (100, $[M+Na]^+$). HR-MS: 267.1405 ($C_{12}H_{24}NaO_3Si^+$; calc. 267.1392).

*Methyl (3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hex-5-enoate* (**5**). To a stirred soln. of **11** (0.32 g, 1.31 mmol) in Et_2O (5 ml), CH_2N_2 in Et_2O was added, until yellow color sustained at 0°, and the mixture was stirred for 5 min. Evaporation of the solvent under reduced pressure and purification of the residue by CC (SiO_2; 2% AcOEt/hexane) afforded **5** (0.28 g, 85%). Yellow oil. $[\alpha]_D^{25} = -68.4$ ($c = 0.55$, $CHCl_3$). IR (neat): 3078, 2932, 2858, 1711, 1644, 1433, 1254, 1090, 834, 776. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.84–5.68 (*m*, 1 H); 5.07 (*s*, 1 H); 5.03–4.99 (*m*, 1 H); 4.17 (*quint.*, *J* = 6.0, 1 H); 3.64 (*s*, 3 H); 2.40–2.38 (*m*, 2 H); 2.27–2.23 (*m*, 2 H); 0.85 (*s*, 9 H); 0.06 (*s*, 3 H); 0.02 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 177.3;

133.7; 118.0; 68.8; 61.5; 41.9; 41.7; 25.6; 17.9; −4.5; −5.01. ESI-MS: 259 (5, $[M+H]^+$), 281 (70, $[M+Na]^+$). HR-MS: 281.1561 ($C_{13}H_{26}NaO_3Si^+$; calc. 281.1548).

*(*tert*-Butyl)(dimethyl){[(1*S*)-1-phenylprop-2-en-1-yl]oxy}silane* (**6**). To a stirred soln. of **8** [7b] (0.25 g, 1.86 mmol) in CH_2Cl_2 (3.5 ml), 1*H*-imidazole (0.25 g, 3.67 mmol) was added at 0°, and the mixture was stirred for 5 min; then, TBS-Cl (0.30 g, 2.04 mmol) was added, and the mixture was stirred for 0.5 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), and the org. layer was washed with H_2O (5 ml), followed by brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2; 1% AcOEt/hexane) to afford **6** (0.37 g, 80%). Colorless oil. $[\alpha]_D^{25} = -46.0$ ($c = 0.25$, $CHCl_3$). IR (neat): 3450, 2930, 2860, 1710, 1676, 1390, 1219, 830. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38 (*d*, *J* = 7.3, 1 H); 7.31–7.17 (*m*, 4 H); 5.95–5.84 (*m*, 1 H); 5.27 (*td*, *J* = 1.3, 16.9, 1 H); 5.15 (*d*, *J* = 5.6, 1 H); 5.04 (*td*, *J* = 1.3, 10.1, 1 H); 0.93 (*s*, 9 H); 0.14 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 141.6; 128.1; 126.9; 125.9; 125.5; 113.3; 75.8; 25.8; 18.3; −4.6; −4.8. ESI-MS: 271 (70, $[M+Na]^+$).

*Methyl (3*R*,5*E*,7*S*)-3,7-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-7-phenylhept-5-enoate* (**4**). To a soln. of **5** (0.24 g, 0.93 mmol) and **6** (0.34 g, 1.37 mmol) in CH_2Cl_2 (5 ml), 10 mol-% *Grubbs*' catalyst II (**A**; 0.078 g, 0.09 mmol) was added and stirred at r.t. for 24 h under N_2. Most of the solvent was then distilled off, and the concentrated soln. was left to be stirred at r.t. for 2 h under air bubbling in order to decompose the catalyst. The mixture was evaporated to dryness to give a brown residue, which was purified by CC (SiO_2; 1% AcOEt/hexane) to give **4** (0.26, 60%) as a yellow color liquid, and *dimethyl (3*R*,5*E*,8*R*)-3,8-bis{(*tert*-butyl)(dimethyl)silyl]oxy}dec-5-enedioate* (**12**) (0.022, 5%) as colorless syrup.

Data of **4**: $[\alpha]_D^{25} = -40.8$ ($c = 0.75$, $CHCl_3$). IR (neat): 3452, 2931, 2857, 1742, 1634, 1253, 1087, 835, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.31–7.16 (*m*, 5 H); 5.72–5.55 (*m*, 1 H); 5.54–5.35 (*m*, 1 H); 5.11 (*d*, *J* = 5.2, 1 H); 4.24–4.12 (*m*, 1 H); 3.64 (*s*, 3 H); 2.47–2.34 (*m*, 2 H); 2.28–2.17 (*m*, 2 H); 0.93 (*s*, 9 H); 0.86 (*s*, 9 H); 0.087 (*s*, 3 H); 0.08 (*s*, 3 H); 0.06 (*s*, 3 H); 0.05 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.1; 137.0; 128.1; 126.8; 125.8; 124.7; 117.7; 75.3; 69.0; 51.4; 41.8; 40.2; 25.6; 25.8;17.9; 17.5; −4.2; −4.5; −4.7; −5.0. ESI-MS: 501 (100, $[M+Na]^+$). HR-MS: 501.2821 ($C_{26}H_{46}NaO_4Si_2^+$; calc. 501.2832).

Data of **12**: $[\alpha]_D^{25} = -53.1$ ($c = 0.5$, $CHCl_3$). IR (neat): 3078, 2932, 2858, 1711, 1644, 1433, 1254, 1090, 834, 776. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.72–5.57 (*m,* 2 H); 4.31 (*quint.*, *J* = 5.8, 2 H); 3.82 (*s*, 6 H); 2.58–2.53 (*m*, 4 H); 2.39 (*t*, *J* = 5.2, 4 H); 1.04 (*s*, 18 H); 0.23 (*s*, 6 H); 0.20 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.3; 129.2; 69.8; 51.8; 42.4; 40.9; 25.8; 18.2; −4.0; −5.1. ESI-MS: 489 (28, $[M+H]^+$), 511 (100, $[M+Na]^+$). HR-MS: 511.2892 ($C_{24}H_{48}NaO_6Si_2^+$; calc. 511.2887).

Conversion of **12** *to* **4**. To a soln. of **12** (0.010 g, 0.02 mmol) and **6** (0.007 g, 0.02 mmol) in CH_2Cl_2 (1 ml), 10 mol-% **A** (0.004 g, 0.047 mmol) was added, and the mixture was stirred at r.t. for 24 h under N_2. Most of the solvent was then distilled off, and the concentrated soln. was left to be stirred at r.t. for 2 h under air bubbling in order to decompose the catalyst. The mixture was evaporated to dryness to give a brown residue, which was purified by CC (SiO_2; 1% AcOEt/hexane) to give **4** (0.005, 60%).

*Methyl (3*R*,5*R*,6*S*,7*R*)-3,7-Bis{[(*tert*-butyl)(dimethyl)silyl]oxy}-5,6-dihydroxy-7-phenylheptanoate* (**3**). To a stirred soln. of **4** (0.24 g, 0.50 mmol) in acetone/H_2O 4:1 (2 ml), NMO (0.11 ml, 1 mmol) and 2 ml of 1M toluene soln. of OsO_4 were added at r.t., and the mixture was stirred for 24 h. The reaction was quenched with Na_2SO_3 (0.2 g), the mixture was filtered and washed with AcOEt, and the resulting filtrate was washed with H_2O (4 ml), followed by brine (4 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2; 5% AcOEt/hexane) to afford **3** (0.19 g, 75%). Syrupy liquid. $[\alpha]_D^{25} = -34.1$ ($c = 0.2$, $CHCl_3$). IR (neat): 3451, 2856, 1739, 1639, 1254, 836, 777, 700. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.57–7.38 (*m*, 5 H); 5.10 (*d*, *J* = 4.5, 1 H); 4.54–4.39 (*m*, 1 H); 4.22 (*d*, *J* = 10.5, 1 H); 3.83 (*s*, 3 H); 3.54–3.43 (*m*, 1 H); 3.38 (br. *s*, OH); 2.70–2.54 (*m*, 3 H); 2.09–1.87 (*m*, 1 H); 1.12 (*s*, 9 H); 0.97 (*s*, 9 H); 0.30 (*s*, 3 H); 0.21 (*s*, 3 H); 0.02 (*s*, 3 H); 0.09 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.3; 141.0; 128.4; 127.6; 126.2; 78.7; 66.6; 65.5; 64.7; 51.4; 42.7; 41.1; 25.9; 25.8; 18.2; 17.9; −4.4; −4.6; −4.77; −5.02. ESI-MS: 513 (42, $[M+H]^+$), 535 (100, $[M+Na]^+$). HR-MS: 535.2891 ($C_{26}H_{48}NaO_6Si_2^+$; calc. 535.2887).

*(4*R*,6*R*)-6-[(1*R*,2*R*)-1,2-Dihydroxy-2-phenylethyl]-4-hydroxytetrahydro-2*H*-pyran-2-one* (**1**). To a stirred soln. of **3** (0.16 g, 0.31 mmol) in MeCN (2 ml), *Amberlyst 15* (0.005 g) was added at r.t. and stirred for 2 h. The mixture was filtered and washed with AcOEt, and the resulting filtrate was evaporated *in vacuo* and purified by CC (SiO_2; 35% AcOEt/hexane) to afford **1** (0.073 g, 93%). Colorless needles. $[\alpha]_D^{25} = -63.1$ ($c = 0.3$, $CHCl_3$). IR (neat): 3423, 2920, 2850, 1720, 1656, 1460, 1219, 606. ^{1}H-NMR

(500 MHz, $CDCl_3$): 7.47–7.25 (*m*, 5 H); 4.91 (*d*, *J* = 7.8, 1 H); 4.73 (*dd*, *J* = 4.4, 9.8, 1 H); 4.28 (*quint.*, *J* = 6.8, 1 H); 3.7 (*d*, *J* = 8.8, 1 H); 2.86 (*dd*, *J* = 5.4, 17.2, 1 H); 2.55 (*dd*, *J* = 7.3, 17.2, 1 H); 2.20–2.14 (*m*, 1 H); 2.08–1.99 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.1; 141.3; 128.5; 127.8; 127.2; 78.0; 68.9; 67.0; 66.8; 41.1; 40.1. ESI-MS: 275 (100, $[M+Na]^+$). HR-MS: 275.0907 ($C_{13}H_{16}NaO_5^+$; calc. 275.0895).

One of the authors, *M. A.*, thanks the *CSIR*, New Delhi, for financial support in the form of fellowship.

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Received September 27, 2010